UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/040,722	01/07/2002	Nelson Ruiz-Opazo	50047/006003	3696

21559 7590 07/03/2002

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	5

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/040,722	Applicant(s) RUIZ-OPAZO, NELSON
	Examiner Brian Whiteman	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 03 April 2002 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claim 1 is pending examination.

Priority

This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior application. The current status of the non-provisional parent application referenced should be included.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

NOTE: In the response, please submit a response to the PTO 498. If the reply to the Non-Final Rejection does not have a response to the 498, the response will be considered non-responsive. See 37 CFR 1.85(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, as best understood, is readable on a genus of a non-human mammal or a transgenic non-human mammal comprising a functional variant hypertension susceptibility gene and/or a genus of a functional variant hypertension susceptibility gene, wherein the genus of a non-human mammal and/or a genus of a functional variant hypertension susceptibility gene is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention encompasses a functional variant hypertension susceptibility gene, said susceptibility gene meets all the following criteria: 1) identification of a functionally significant structural mutation in the relevant gene: criteria 2), concordance of the observed genetic dysfunction with a pathophysiologic mechanism logical to the hypertension pathogenesis; criteria 3), association of the putative hypertension susceptibility gene with hypertension in validated genetic animal models or human hypertensive patients; and criteria 4), delineation of the mechanistic role in an in vivo model (Herrera, *J. Clin. Invest.*, Vol. 102, 1998, pg. 1102). The genus of a susceptibility hypertension gene is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

The specification displays data to support the α1 Na,K-ATPase gene as a susceptibility gene for salt-sensitive hypertension Dahl S rat, wherein the gene meets the following criteria listed above. However, it is apparent that on the basis of the applicant's disclosure, an adequate

written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a non-human mammal or transgenic non-human mammal comprising a functional variant hypertension susceptibility gene and/or a functionally variant hypertension susceptibility gene expressed as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of a non-human mammal and/or a transgenic non-human mammal comprising a functional variant hypertension susceptibility gene and/or a genus of hypertension susceptibility genes that must exhibit the disclosed biological functions as contemplated by the claims.

The as-filed specification does not provide sufficient support for the present claimed invention directed to a genus of a non-human mammal comprising a functional variant hypertension susceptibility gene and/or a genus of a hypertension susceptibility gene, except for the α1 Na,K-ATPase gene in the salt-sensitive hypertension Dahl S rat. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of a non-human mammal and/or a transgenic non-human mammal comprising a functional variant hypertension susceptibility gene and/or a genus of functionally variant hypertension susceptibility gene that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be

shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a predictable representative number of species of the claimed non-human mammal and/or a transgenic non-human mammal and/or a hypertension susceptibility gene that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claim 1, as best understood, is rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabled for:

1) A method of assaying a test compound, said method comprising:

a) providing a Dahl Salt-sensitive^{HSD} rat or a transgenic rat whose genome comprises the hypertension susceptibility α1 Na,K-ATPase gene coding for the Sα1 nucleic acid sequence (as shown in Herrera et al., *Science*, Vol. 249, pp. 1024 and 1025, 1990),

In order for one skilled in the art to understand what the amino acid substitution (Q276L) and the nucleotide substitution T^{1079} for A^{1079} are relative to in the rat's genome. The applicants are required to submit a sequence ID listing for the amino acid sequence and the nucleotide sequence for α1cRNA and α1 cDNA, respectively.

Furthermore, when submitting an amino acid and/or a nucleotide sequence for examination. The applicants are reminded to follow the USPTO guidelines under sequence rules (37 CFR 1.821 - 1.825).

b) administering the test compound to the rat in step a); and

c) determining whether the test compound modulates hypertension parameters in the rat relative to the hypertension parameters in a rat containing a wild-type α1 Na,K-ATPase gene.

The as-filed specification does not reasonably provide enablement for the presently pending claims encompassing any other functionally variant hypertension susceptibility gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with this claim.

Specifically, since the claimed invention is not supported by a sufficient description (for possessing a genus of a non-human mammal comprising a functional variant hypertension susceptibility gene and/or a genus of functionally variant hypertension susceptibility gene) as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, *e.g.* a method of assaying a test compound, using a non-human mammal with a functionally variant hypertension susceptibility gene.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention relates to a method of a method of assaying a test compound, said method comprising: a) providing a non-human mammal with a functionally variant hypertension susceptibility gene, b) administering said test compound to said non-human mammal, and c) determining whether said test compound affects hypertension parameters in said non-human animal relative to a non-human mammal containing a wild-type hypertension susceptibility gene. The claimed invention lies in the field of using a non-human mammal comprising a functionally variant hypertension susceptibility gene. In addition, in view of the as-filed specification, the claimed invention also lies in the field of using a transgenic non-human mammal comprising a heterologous functionally variant hypertension susceptibility gene.

Even if the applicant is able to overcome the 112 written description for a genus of hypertension susceptibility gene and/or a transgenic non-human mammal and/or non-human mammal, there are still concerns set forth by the state of the art for predicting a protein's tertiary structure based on its polypeptide sequence, identifying hypertension genes, and the production of transgenic non-human mammals.

The state of the art for hypertension, as exemplified by Herrera et al., J. Clin. Invest. Vol. 102, 1998, pp. 1102-1111, display that:

> Essential hypertension (EHT) is a paradigmatic, complex, and multifactorial condition. Genes that mediate EHT will therefore be difficult to isolate and characterize, requiring multiple lines of evidence to prove their roles in EHT pathogenesis. Cognizant of these issues, delineation of a putative EHT susceptibility gene should meet the following criteria set forth on page 1102, right column, 1st paragraph. See page 1102.

In addition, the state of the art in 1998 for predicting tertiary structure (biological activity) from a polypeptide sequence, as exemplified by Chiu et al., *Folding and Design*, Vol. 3, pg. 223-228, May 1998, displays major consideration for predicting a protein tertiary structure involve issues that include:

> Predicting the three-dimensional conformation of a correctly folded protein can be divided into two distinct steps: the construction of a fitness function to evaluate the various conformations: and the search through various possible conformations for the "best" prediction most likely to represent the native state. Neither part of this problem has proven particularly tractable. The development of a general method for the prediction of protein tertiary structure based on the protein sequence remains, unfortunately, one of the great-unsolved problems of computational biophysics (pg. 223).

Furthermore, with respect to the state of the art for transgenic non-human animals, the starting material for the method is a non-human animal and the transgenic animal would require the production of transgenic non-human animals encompassing the use of embryonic stem (ES) cell technology or using pro-nuclear injection. The state of the art at the time application was filed for producing transgenic animals using pro-nuclear injection was considered unpredictable as exemplified by Polejaeva et al. Theriogenology, Vol. 53, pages 117-126, 2000, Polejaeva states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's

> health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could require undue experimentation. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke et al. disclose, "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Reprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

> The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

Therefore, the art of record for the production of transgenic non-human animals is considered unpredictable at the time the invention was filed.

The as-filed specification discusses that the invention features a genus of a non-human mammal comprising a susceptibility hypertension gene. The specification provides working examples encompassing the production of a transgenic rat using microinjection of a nucleic acid encoding alpha1 NA, K-ATPase protein and methods of studying a high salt diet using the transgenic rats (pages 8-24).

Furthermore, with respect to the claimed invention encompassing a functionally variant hypertension susceptibility gene, the as-filed specification provides description of a Dahl Salt Sensitive^{HSD} rat or a transgenic rat that has a susceptibility hypertension gene (α1 Na,K-ATPase). However, the prior art teaches that essential hypertension (EHT) is a paradigmatic complex and multifactorial condition (Herrera et al., *J. Clin. Invest*, Vol. 102, 1998, pg. 1102-1111). Genes that mediate EHT will therefore be difficult to isolate and characterize, requiring multiple lines of evidence to prove their roles in EHT pathogenesis (page 1102). With respect to Herrera, it is not apparent how the disclosure is enabled for any other hypertension susceptibility gene (except the α1 Na,K-ATPase gene in Dahl Salt Sensitive rat) in any other non-human mammal. The essential feature of the claimed invention is the requirement of staring material (e.g. a non-human mammal or a transgenic non-human mammal comprising a hypertension susceptibility gene). It is not apparent how to make any other non-human mammal with a functionally variant hypertension susceptibility gene other than the α1 Na,K-ATPase gene in the salt-sensitive hypertension Dahl S rat due to the reasons set forth above. More specifically as to the lack of reasonable extrapolation from the biological functional of the hypertension susceptibility gene to that of any other functional variant, it would take one skilled in art an undue amount of experimentation to make and/or use the claimed invention. Especially with lack of sufficient guidance required for predicting any protein tertiary structure based on a protein structure. At the time the application was filed, predicting any protein tertiary structure based on a protein structure was considered to be unpredictable due to significant problems in several areas (see Chui et al.).

Thus, given the lack of sufficient guidance cited in the claims and state of the art, one would have to engage in a large quantity of experimentation in order to practice the full breath of the claimed invention on the basis of applicant's disclosure. It is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of any hypertension susceptibility gene to the full scope of the claimed invention. Even if it has been shown that the Dahl Salt Sensitive^{HSD} rat has a susceptibility hypertension gene (α1 Na,K-ATPase). It is not apparent as to how the experimental result is reasonably extrapolated to the full scope of the claimed invention encompassing any other hypertension susceptibility gene, except the α1 Na,K-ATPase gene in Dahl Salt Sensitive^{HSD} rat, which is not a general phenomenon, and given the doubts expressed in the art of record.

Even if the applicants overcome the 112 enablement for making and/or using a non-human mammal comprising a hypertension gene, the state of the art for producing a transgenic non-human mammal is considered unpredictable. With respect to claim 1, as the claimed invention encompass a transgenic non-human animal comprising a hypertension susceptibility gene using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic non-human male animal, the state of the art supports that only mouse ES cells were enabled for use in the production of transgenic mice. In view of the concerns set forth by the state of the art, the examples do not reasonably address the concerns put forth by the state of the art encompassing any method for producing transgenic male non-human animals for use in a method of assaying a test compound. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate from the specification and the prior art to any transgenic male non-human animal

comprising a hypertension susceptibility gene in its genome. In addition, in view of the concerns stated above encompassing microinjection and random integration into a mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from random integration to determining if a transgene is inserted at the correct site and is expressed at a level sufficient enough for use in a method of assaying a test compound that modulates hypertension in a mammal.

As the as-filed specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human mammals as claimed, one skilled in the art would not be able to rely on the state of the art for an attempt to produce any transgenic non-human mammals other than the rat. This is because of the art of transgenic is not predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mammal comprising a transgene of interest (e.g. hypertension susceptibility gene); it is not predictable if the transgene would be expressed at a level and specificity sufficient to be used in a method of assaying a test compound that modulates hypertension. For example, the level and specificity of expression of a transgene (e.g. hypertension susceptibility gene) as well as the resulting phenotype of the transgenic non-human mammal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified non-human animals, which exhibit a particular phenotype (hypertension). This observation is supported by Wall (Theriogenology, 1996) who states "Our

understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report "transgene expression and the physiological consequences of transgene in animals are not always predicted in transgenic mouse studies." See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 239-239). Therefore, the state of the art teaches that the production of transgenic non-human animals is considered unpredictable.

Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic non-human animal that expresses a hypertension susceptibility gene other than a rat, it would require an undue amount of experimentation to reasonably predict the results achieved in

any transgenic non-human animal comprising a transgenic sequence encoding a hypertension susceptibility gene and which expresses the protein in the transgenic non-human animal at the levels of the claimed product, the consequences of that production, and therefore, the resulting use in any method of assaying a test compound that could modulate hypertension.

In addition, the disclosure fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic non-human animals comprising a hypertension susceptibility gene. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any contemplated transgenic animal of the invention other than a transgenic rat. Thus, as enablement requires the specification to teach how to make and/or use the claimed invention, the specification fails to enable the production of any transgenic non-human animal comprising a hypertension susceptibility gene other than a transgenic rat.

[Note that although the claimed transgenic mammal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic male non-human animal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mammal would serve if the transgene (e.g. hypertension susceptibility gene) is not expressed at a sufficient level for a resulting phenotype).]

Thus, in view of the In re Wands' Factors, the disclosure is enabled only 1 listed above and is not enabled for the full scope of the claimed invention because in view of the undue quantity of experimentation necessary to determine the parameters listed above for the starting material (non-human mammal or transgenic non-human mammal), the lack of direction or sufficient guidance provided by the as-filed specification for the production of any transgenic non-human mammal or non-human mammal with a particular phenotype other than a rat. Furthermore, the lack of working examples for the demonstration or the reasonable correlation to the production of any transgenic non-human mammal, in particular when the expression of the must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human mammals of any species other than rat, and the breadth of the claims drawn to any transgenic non-human mammal or non-human mammal, it would require an undue amount of experimentation for one skilled in the art to make and/or use the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: said hypertension parameters in a non-human mammal. Without recitation of the essential step and the necessary structural cooperation relationships of the

material necessary to practice the claimed invention, the metes and bounds of the claim is not apparent, and thus, the claim when read as a whole fails to point out and distinctly claim the invention. It is not apparent what is being compared in claim 1 between the hypertension parameters in said non-human mammal relative to a non-human mammal containing a wild type gene. Claim 1 should recite "hypertension parameters in said non-human mammal relative to said hypertension parameters in a non-human mammal.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

To the extent that claim 1 is enabled for:

A method of assaying a test compound, said method comprising:

a) providing a Dahl Salt-senstive^{HSD} rat or a transgenic rat whose genome comprises the hypertension susceptibility α1 Na,K-ATPase gene coding for the Sα1 nucleic acid sequence (as shown in references (6) and (7) of Herrera et al., *Science*, Vol. 249, pp. 1024 and 1025, 1990),

b) administering said test compound to said rat, and

c) determining whether said test compound modulates hypertension parameters in said rat relative to said hypertension parameters in a rat containing a wild-type α1 Na,K-ATPase gene, the following rejection applies:

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Medvedev et al. (*J. Auton. Nerv Syst*, Vol. 72, 1998, pp. 170-6); Vesely (US Patent 5,691,310); or Somova et al. (*Methods Find Exp Clin Pharamcol*, Vol 21, 1999, pp. 412-5) taken with Herrera et al., (*J. Clin. Invest.* Vol. 102, 1998, pp. 1102-1111). Somova teaches a method to evaluate glucose metabolism and insulin sensitivity in the Dahl genetic salt-sensitive rat model of hypertension (abstract). Vesely teaches that in vivo animal testing demonstrate that potent natriuretic, diuretic, and blood pressure reducing effects exhibited by two peptide hormones originating for the human atrial factor (ANF) prohormone consisting of amino acid 1-30 and 31-67 of the human prohormone while another peptide hormone consisting of amino acids 79-98 of the human ANF prohormone has diuretic, kaliuretic and blood pressure lowering properties (columns 3, lines 61-66 and column 4, lines 1-5). In addition, Medvedev investigated the chronopharmacological dependence of dose-dependent hypotensive and cardiochronotropic effects of the imidazoline-like drugs in stroke-prone spontaneously hypertensive rats (abstract). However, Somova, Vesely, or Medvedev do not describe a method of assaying a chemical compound using a Dahl Salt-sensitive^{HSD} rat or transgenic rat whose genome comprises susceptibility hypertension gene (α1 Na,K-ATPase gene).

However, at the time the invention was made, Herrera displayed a Dahl Salt-sensitive^{HSD} rat and a transgenic rat with the susceptibility hypertension gene (α1 Na,K-ATPase gene) in its genome.

At the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill, as a matter of obvious design choice to combine the teaching of either Somova, Vesely, or Medvedev taken with Herrera to test chemical compounds in Dahl Salt-senstive^{HSD}

rats or transgenic rat with the α1 Na,K-ATPase gene. One of ordinary skill in the art would have been motivated to study how chemical compounds modulate hypertension parameters in the Dahl Salt-sensitive^{HSD} rat or transgenic rat with the α1 Na,K-ATPase gene particularly since assaying chemical compounds in hypertensive rats was well known in the art as taught by either Somova or Medvedev.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1635
6/26/02